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PROSTATE BIOPSY FOLLOWING A POSITIVE SCREEN IN THE PROSTATE, LUNG, COLORECTAL AND OVARIAN CANCER SCREENING TRIAL

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ABSTRACT

Purpose: The benefit of prostate specific antigen (PSA) and digital rectal examination (DRE) screening for prostate cancer is under evaluation in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Followup of positive screens in PLCO is done by subject personal physicians and it is outside of trial control. We describe the pattern of prostate biopsy in men with positive screens in PLCO.

Materials and Methods: We examined all men with positive baseline PSA or DRE screens and men with positive post-baseline screens occurring by December 2000.

Results: Of 2,717 men with positive PSA (greater than 4 ng/ml) at baseline 41% and 64% underwent biopsy within 1 and 3 years, respectively. A screening PSA of 7 to 10 and greater than 10 ng/ml at baseline was associated with significantly higher biopsy rates (HR 1.9 and 2.6, respectively) compared to PSA 4 to 7 ng/ml. The 1,793 in men whom the first positive PSA was after baseline had a lower overall biopsy rate (50% within 3 years). Furthermore, PSA above 7 ng/ml were not associated with higher biopsy rates in this group. The 4,449 men with positive DRE screens and negative PSA had a 3-year biopsy rate of 27%. Men with positive DRE at diagnostic followup had a biopsy rate of around 90%. However, few men, even of those with positive DRE screens, had positive diagnostic DREs.

Conclusions: These biopsy rates following positive PSA and DRE screens are likely to be representative of national rates. These results suggest that PLCO is evaluating the effects of screening in a contemporary and robust manner.

KEY WORDS: prostate, prostatic neoplasms, biopsy, mass screening, prostate-specific antigen

Prostate cancer incidence increased dramatically in the 1980s and early 1990s, and then began decreasing around 1993.[1] Researchers have attempted to link these secular trends in prostate cancer incidence with trends in prostate specific antigen (PSA) testing, which became widespread in the early 1990s.[2,3] The impact of PSA screening on the prostate cancer incidence is mediated through prostate biopsy. The combination of screening rates, test positivity rates and rates of biopsy in screening positive men contribute to the prostate cancer incidence.

The prostate component of the ongoing multicenter Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial was designed to test whether screening with PSA and digital rectal examination (DRE) decreases prostate cancer mortality.[4] The design of PLCO is such that diagnostic followup is outside of the control of the trial and, thus, decisions on diagnostic followup of positive PLCO screens occur independently at hundreds of physician offices and health plans throughout the country. There are currently little nationally representative data on prostate biopsy rates in men being assessed for suspicious prostate cancer screening tests, although some data are available from the Prostate Cancer Awareness Week cohort.[5] In this study we examined biopsy rates following a positive screen in men enrolled in the intervention arm of the PLCO trial. In addition, we analyzed the effect of various factors, including demographics, medical and screening history, screening PSA and the results of nonbiopsy diagnostic procedures, on the likelihood of prostate biopsy following a positive screen.

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METHODS

The PLCO Cancer Screening Trial is a multicenter, randomized, controlled trial designed to test the effect of screening for 4 types of cancer in men who are 55 to 74 years old at baseline.[4] Randomization to a screened or control arm was done between November 1993 and July 2001 with almost 155,000 individuals randomized. Men in the screening arm undergo PSA testing and DRE at baseline (year 0), annually through year 3 and then PSA testing without DRE at years 4 and 5. Men in the screening arm also undergo flexible sigmoidoscopy and chest x-ray. Exclusion criteria are a history of prostate, lung or colorectal cancer, surgical removal of the entire prostate, having received finasteride in the last 6 months and starting in 1995 having undergone more than 1 PSA blood test in the last 3 years. Around the time of randomization subjects completed a self-administered demographic and medical/screening history questionnaire.

PSA tests were performed at a single laboratory using a Hybritech assay (Hybritech Beckman Coulter Corp., San Diego, California). A PSA result of greater than 4 ng/ml was considered positive. DRE was performed by a qualified ex-

aminer (physician, nurse or physician assistant). Men were referred to private physicians or health plans for positive screen followup. The PLCO trial did not recommend a diagnostic algorithm. PLCO obtained medical records related to the diagnostic followup of positive screens and trained medical record abstractors recorded information on diagnostic procedures. Abstractors recorded the result of diagnostic PSA tests throughout the study period. The results of other diagnostic tests were obtained only in the first few years of the trial.

The cohort used in this analysis consisted of all men with a positive year 0 PSA or DRE screen plus all who had a positive PSA or DRE screen at study years 1 to 3 by December 31, 2000. Diagnostic procedures, including biopsy, were examined for a 3-year period following the first instance of a positive screen.

Statistical methods. Kaplan-Meier survival curves were used to estimate the probability of first undergoing any diagnostic procedure or prostate biopsy as a function of time since the first positive screen.[6] Cox proportional hazards regression was used to assess simultaneously the influence of various factors on the probability (hazard) of first undergoing any diagnostic procedure or prostate biopsy.[7] Subjects were treated as censored when no further information about diagnostic followup was available. When modeling the hazard for any diagnostic procedure, separate models were run for men with PSA positive and with DRE only positive results. For prostate biopsy men with baseline PSA positive results differed considerably from those with post-baseline PSA positive results. Thus, separate models were run for men with baseline PSA positive, post-baseline PSA positive and DRE positive results.

RESULTS

A total of 4,801 men had abnormal DRE or PSA at the baseline screen, of whom 2,717 had abnormal baseline PSA. There were 4,158 additional men who first had abnormal PSA or DRE at years 1 through 3, of whom 1,793 had abnormal PSA. Table 1 shows the distribution of various demographic, medical history and screening factors by type of abnormal test (DRE only or PSA) and study year of the abnormal test (baseline or after baseline). Men with positive PSA at baseline were more likely to have undergone prior prostate biopsy and have a history of prostate problems, screening PSA above 7 ng/ml and a positive screening DRE than men who were first PSA positive after baseline.

TABLE 1. *Factors by type and study year of first abnormal screen*

	% PSA Pos		% Pos DRE Only	
	Baseline	After Baseline	Baseline	After Baseline
No. subjects	2,717	1,793	2,084	2,365
Prostate Ca family history	9	8	8	7
Prior biopsy*	18	5	11	6
Prostate problem history*	44	31	37	30
Prior PSA*	49	51	51	49
Prior DRE*	60	66	64	63
Age:				
55–59	16	18	21	19
60–64	29	26	31	29
65–69	32	34	28	29
70 or Older	23	22	20	23
Race:				
Black	5.6	5.8	3.1	3.0
Hispanic	1.5	1.8	1.8	1.4
Asian	3.7	3.4	2.1	1.9
Yr 1993–1996	60	21	59	22
PSA 2.5–4.0 ng/ml	—	—	17	16
Pos DRE	15	7	—	—
PSA 7–10 ng/ml	17	7	—	—
PSA greater than 10 ng/ml	13	4	—	—

* Prior to randomization into PLCO trial.

Kaplan-Meier analysis. Table 2 lists the cumulative probability of undergoing any followup diagnostic procedure and prostate biopsy within 1 to 3 years of the first positive screen by type of abnormal screening test and study year, as estimated from the Kaplan-Meier survival curves. The rate of any diagnostic procedure differed little by test type and study year. Overall 79% and 89% of men underwent a diagnostic procedure within 1 and 3 years, respectively, of the first positive screen. The highest biopsy rates were observed in the men with baseline PSA positive results (64% by year 3), followed by those with post-baseline PSA positive results (50% by year 3) and DRE positive results (27% to 28% by year 3).

Figures 1 and 2 show biopsy rates by PSA in men with positive PSA at and after baseline, respectively. In men with baseline positive results the 3-year biopsy rate increased greatly with the screening PSA level, going from 58% for PSA 4 to 7 ng/ml to 77% for PSA 7 to 10 ng/ml to 85% for PSA greater than 10 ng/ml (fig. 1). In men with positive PSA after baseline differences across screening PSA levels were muted (fig. 2). Men with a screening PSA of 4 to 7 ng/ml had a 3-year biopsy probability of 50% compared with a 3-year probability of 55% in men with a PSA of 7 to 10 ng/ml. Men with screening PSA greater than 10 ng/ml actually had the lowest biopsy rate, that is 47% by year 3.

Cox regression. Table 3 shows Cox regression results for any diagnostic procedure. In men with positive PSA, post-baseline positive screen year, positive screening DRE and high screening PSA had significantly increased hazards ratios for any diagnostic procedure. HRs of 1.3 and 1.5 were observed for screening PSA 7 to 10 and greater than 10 ng/ml, respectively (compared to 4 to 7 ng/ml) and an HR of 1.5 was observed for positive DRE. A history of prostate biopsy, older age, Hispanic and Asian ethnicity, and calendar year 1993 to 1996 had an HR of significantly below 1.0. In men with DRE positive results screening PSA 2.5 to 4.0 ng/ml, a post-baseline year of the first positive screen and prior DRE each had a significantly elevated HR (1.16, 1.15 and 1.10, respectively), while calendar year 1993 to 1996 had a significantly decreased HR (0.83).

Table 4 lists Cox regression results for prostate biopsy. In men with baseline PSA positive results prior prostate biopsy, prior PSA, a history of prostate problems and older age were significantly associated with lower biopsy rates (HR 0.75 to 0.85). Increased screening PSA, screen DRE positivity and prior DRE were significantly associated with higher biopsy rates. The HRs for increased PSA were 1.9 and 2.6 for PSA 7 to 10 and greater than 10 ng/ml, respectively, while the HR for positive DRE was 1.8. In men with post-baseline PSA positive results neither increased PSA screening levels nor prior biopsy, prior PSA or a history of prostate problems were significantly associated with prostate biopsy. DRE screen positivity had a significantly increased HR in these men (2.1). In men with positive DRE screening PSA 2.5 to 4.0 ng/ml (HR 1.9) and Asian ethnicity (HR 1.8) were associated with a significantly increased biopsy rate, while older age was associated with a significantly decreased biopsy rate (HR 0.8).

Diagnostic PSA and DRE, and prostate biopsy. Table 5 shows 1-year biopsy rates according to the occurrence and outcome of various diagnostic tests in men with any diagnostic procedure within a year of their positive screen. The biopsy rate in men with baseline PSA positive results was lower in those with diagnostic PSA but no diagnostic DRE performed (26%) than in those with diagnostic DRE and PSA (49%) or those with diagnostic DRE and no diagnostic PSA (68%). The corresponding biopsy rates in men with post-baseline positive PSA were 10% (diagnostic PSA only), 35% (diagnostic PSA and DRE) and 71% (diagnostic DRE only). Of those with baseline plus post-baseline PSA positive

TABLE 2. *Probability of any diagnostic procedure and prostate biopsy after positive screen*

Time From Pos Screen 1 (yr)	% Yr 1 (95% CI)	% Cumulative Yr 2 (95% CI)	% Cumulative Yr 3 (95% CI)
Any procedure:			
DRE pos, PSA neg (0)	75 (73–77)	82 (80–84)	86 (84–88)
DRE pos, PSA neg (1–3)	81 (79–83)	84 (82–86)	85 (83–87)
PSA pos (0)	78 (76–80)	89 (87–90)	94 (92–95)
PSA pos (1–3)	83 (81–85)	89 (87–90)	94 (92–95)
Any pos (0–3)	79 (78–80)	86 (85–87)	89 (88–90)
Prostate biopsy:			
DRE pos, PSA neg (0)	19 (17–21)	24 (22–26)	27 (25–29)
DRE pos, PSA neg (1–3)	22 (20–24)	26 (24–28)	28 (26–30)
PSA pos (0)	41 (39–43)	56 (54–58)	64 (62–66)
PSA pos (1–3)	34 (32–37)	44 (42–47)	50 (47–53)

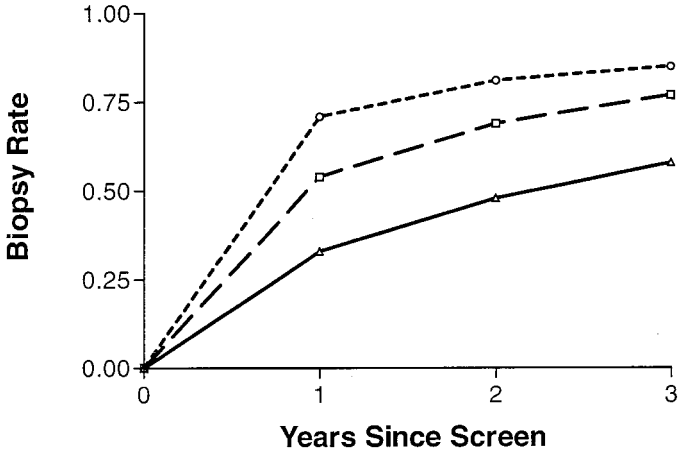

FIG. 1. Cumulative biopsy rates in men with positive baseline PSA by screening PSA level. Dotted line indicates PSA greater than 10 ng/ml. Dashed line indicates PSA 7 to 10 ng/ml. Solid line indicates PSA 4 to 7 ng/ml.

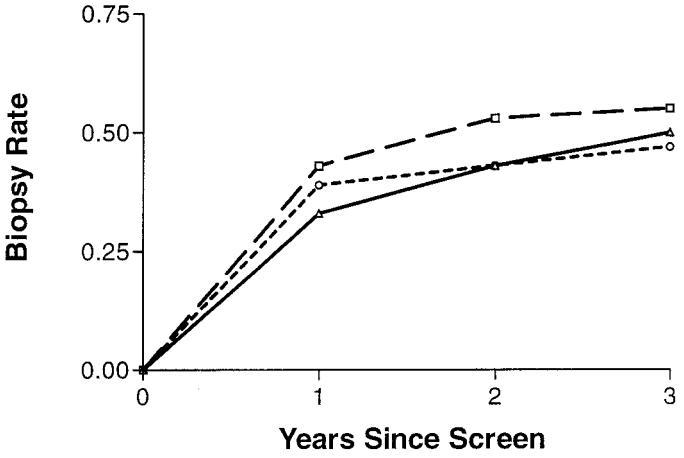

FIG. 2. Cumulative biopsy rates in men with positive post-baseline PSA by screening PSA level. Dotted line indicates PSA greater than 10 ng/ml. Dashed line indicates PSA 7 to 10 ng/ml. Solid line indicates PSA 4 to 7 ng/ml.

TABLE 3. *Any diagnostic procedure Cox regression model*

	HR (95% CI)	
	Pos PSA	Pos DRE, Neg PSA
Prostate Ca family history	1.01 (0.93–1.11)	0.99 (0.89–1.1)
Prior prostate biopsy	0.88 (0.80–0.98)	0.92 (0.81–1.05)
Prostate problem history	1.00 (0.92–1.07)	0.98 (0.91–1.06)
Prior PSA	0.98 (0.91–1.05)	1.07 (0.99–1.15)
Prior DRE	1.08 (1.00–1.16)	1.10 (1.02–1.19)
Yr 1993–1996	0.88 (0.82–0.95)	0.83 (0.77–0.90)
Study yr 1–3 vs 0	1.18 (1.09–1.26)	1.15 (1.07–1.24)
Age:		
55–59	1.0	1.0
60–64	0.97 (0.88–1.07)	0.99 (0.9–1.09)
65–69	0.90 (0.82–0.99)	0.97 (0.87–1.07)
70 or Older	0.87 (0.78–0.96)	0.93 (0.84–1.04)
Race:		
White	1.0	1.0
Black	0.94 (0.82–1.07)	0.82 (0.67–1.0)
Hispanic	0.75 (0.58–0.97)	0.85 (0.65–1.11)
Asian	0.81 (0.68–0.96)	1.18 (0.93–1.49)
PSA 2.5–4.0 vs greater than 2.5 ng/ml		1.16 (1.06–1.27)
Pos DRE	1.5 (1.3–1.6)	
PSA 7–10 vs 4–7 ng/ml	1.3 (1.2–1.4)	
PSA greater than 10 vs 4–7 ng/ml	1.5 (1.4–1.7)	

results about 75% had diagnostic DRE performed (with or without PSA). A relatively small number underwent biopsy as the initial procedure.

The outcome of the diagnostic PSA or DRE had a substantial impact on biopsy rates. Of men with baseline (screen) PSA positive results those with positive (greater than 4 ng/ml) diagnostic PSA had a biopsy rate of 52%, while those with negative diagnostic PSA had a 7% biopsy rate (table 5). A similar biopsy rate pattern for positive vs negative diagnostic PSA outcome was observed in men with post-baseline (screen) PSA positive results (45% vs 7%) and with (screen) DRE positive results (55% vs 20%). However, the percent of diagnostic PSAs that were positive was much lower in men with positive DRE (5%) than in those with positive post-baseline PSA (53%) or positive baseline PSA (81%). Men with positive diagnostic DRE had a biopsy rate of around 90%, although a low percent of men had positive diagnostic DRE (15% to 23%). The biopsy rate in men with negative diagnostic DRE was 35% to 44% for (screen) PSA positive results but only 9% for (screen) DRE positive results.

DISCUSSION

In this analysis we examined prostate biopsy rates following a positive PSA or DRE screen in men enrolled in the PLCO trial. Since diagnostic followup occurred beyond the control of PLCO and was done at numerous sites across the country as part of a pragmatic study design, these results are likely representative of clinical practice in response to positive PSA and DRE screens in the United States during this period (1993 to 2001). Of men with a positive PSA screen at baseline 41% underwent biopsy within 1 year and 64% underwent biopsy within 3 years of the screen. The biopsy rate in men in whom the (first) positive PSA was after baseline was somewhat lower. The biopsy rate in men with positive DRE (but not positive PSA) at baseline was 27% to 28% after 3 years. In a study of 116,073 men who were 40 to 79 years old, screened during Prostate Cancer Awareness Week from 1992 to 1995 and had valid PSA and DRE results Crawford et al reported that 15.6% with abnormal DRE alone, 19.4% with abnormal PSA (greater

TABLE 4. *Prostate biopsy Cox regression model*

	Pos PSA HR (95% CI)		Baseline/Post-Baseline Pos DRE, Neg PSA HR (95% CI)
	Baseline	After Baseline	
Family history	1.14 (1.00–1.30)	1.3 (1.08–1.57)	1.08 (0.91–1.28)
Prior biopsy	0.78 (0.67–0.90)	0.98 (0.72–1.33)	0.84 (0.66–1.07)
Prostate problem history	0.85 (0.75–0.95)	0.88 (0.75–1.02)	0.95 (0.83–1.09)
Prior PSA	0.81 (0.72–0.92)	1.05 (0.91–1.22)	1.02 (0.9–1.16)
Prior DRE	1.13 (1.01–1.27)	0.97 (0.84–1.14)	0.99 (0.87–1.13)
Yr 1993–1996	1.02 (0.92–1.14)	1.0 (0.85–1.19)	0.95 (0.82–1.09)
Study yr 1–3			1.02 (0.9–1.16)
Age:			
55–59	1.0	1.0	1.0
60–64	1.04 (0.9–1.21)	1.3 (1.04–1.55)	0.97 (0.82–1.15)
65–69	0.88 (0.75–1.02)	0.93 (0.77–1.14)	1.04 (0.88–1.24)
70 or Older	0.75 (0.64–0.89)	0.81 (0.63–0.99)	0.80 (0.66–0.97)
Race:			
White	1.0	1.0	1.0
Black	0.99 (0.81–1.22)	1.09 (0.83–1.45)	0.93 (0.66–1.07)
Hispanic	0.82 (0.55–1.23)	0.75 (0.43–1.3)	0.68 (0.4–1.2)
Asian	0.84 (0.63–1.11)	0.76 (0.51–1.14)	1.8 (1.3–2.5)
PSA 2.5–4.0 vs less than 2.5 ng/ml		—	1.9 (1.7–2.2)
Pos DRE	1.8 (1.6–2.0)	2.1 (1.7–2.6)	—
PSA 7–10 vs 4–7 ng/ml	1.9 (1.7–2.1)	1.3 (0.98–1.6)	—
PSA 10 or greater vs 4–7 ng/ml	2.6 (2.3–3.0)	0.96 (0.66–1.4)	—

TABLE 5. *Biopsy rate by diagnostic DRE and PSA test occurrence and results*

Diagnostic Test*	Pos PSA Screen (% biopsy, cohort proportion)		Pos DRE, Neg PSA Screen (% biopsy/cohort proportion)
	Baseline	After Baseline	
No. subjects†	2,113	1,467	3,462
Performed:			
PSA, no DRE	26/0.15	10/0.20	12/0.04
No PSA, DRE	68/0.32	71/0.26	28/0.62
PSA, DRE	49/0.41	35/0.47	24/0.26
Other	28/0.08	30/0.04	10/0.06
Biopsy as first procedure	100/0.05	100/0.03	100/0.01
Outcome:			
Pos PSA	52/0.81	45/0.53	55/0.05
Neg PSA	7/0.19	7/0.47	20/0.95
Pos DRE	91/0.23	91/0.15	87/0.22
Neg DRE	44/0.77	35/0.85	9/0.78

Percent biopsy within 1 year of screen.

* Within 1 year of screen excluding tests after biopsy and outcome is for last test if multiple tests were performed.

† Number with any diagnostic procedure within 1 year of screen.

than 4 ng/ml) alone, and 33.2% with abnormal PSA and DRE underwent prostate biopsy.[5] This compares to biopsy rates in the current study of 19% (abnormal DRE alone), 38% (abnormal PSA alone) and 61% (each abnormal) based on 1-year followup after a positive baseline screen. In the PSA-2 screening study of almost 20,000 men 50 years and over in the St. Louis area from 1991 to 1996, 78% with abnormal initial DRE or PSA (greater than 4 ng/ml) screens underwent recommended biopsy.[8] In a longitudinal continuation of that study Catalona et al reported a 60% compliance rate with the biopsy recommendation in men 50 years and older who were not at high risk and had abnormal PSA or DRE.[9]

We identified various factors that affect the biopsy rate following a positive PSA or DRE screen. In men with positive DRE (and negative PSA) a PSA screening value of 2.5 to 4.0 ng/ml (compared to less than 2.5) was associated with an increased biopsy rate. In men with positive PSA the effect of several factors depended on whether results were first positive at or after baseline. Prior prostate biopsy, prior PSA tests and a history of prostate problems were significantly associated with a lower biopsy rate only in men PSA that was positive at baseline. Additionally, a PSA screening level of 7 to 10 and greater than 10 ng/ml at baseline was associated with an increased biopsy rate (HR 1.9 and 2.6, respectively), while such PSA levels after baseline had an HR for biopsy of almost 1. This finding appears to be related to the reproducibility of increased screening PSA. In the baseline PSA positive group in men with repeat diagnostic PSA within 1 year of the screen the percent who had positive (greater than 4 ng/ml) repeat PSA increased with the screening PSA level from 76% for screening PSA 4 to 7 ng/ml to 89% and 94% for screening PSA 7 to 10 and greater than 10 ng/ml, respectively. No such trend was seen in post-baseline PSA positive results, in which the percent of men with positive diagnostic PSA was 54%, 59% and 43% for screening PSA 4 to 7, 7 to 10 and greater than 10 ng/ml, respectively. The lower overall reproducibility of a positive PSA screen in the post-baseline vs baseline groups probably also explains the fact that the former had a lower overall biopsy rate than the latter. Note that the difference between the post-baseline and baseline PSA positive groups is that the former were restricted to having had a PSA of below 4 ng/ml 1 to 3 years prior to the positive PSA screen, while the latter were not.

Recently Eastham et al reported that a high proportion of men with abnormal PSA had normal PSA at 1 or more subsequent visits during a 4-year followup.[10] They concluded that "an isolated elevation in PSA should be confirmed several weeks later before proceeding with further testing, including prostate biopsy."[10] We found that repeat PSA was performed before deciding on biopsy in 57% and 68% of men with baseline and post-baseline PSA positive results.

Positive diagnostic DRE was associated in this study with a high biopsy rate but it was a relatively infrequent occurrence. The low positivity rate on diagnostic DRE even in men with positive screening DRE (22%) may be partially explained by the fact that PLCO DRE examiners were generally not physicians and they may have been overly conservative in calling borderline findings positive, while diagnostic DREs were presumably performed by internists or urologists.

A limitation of this study is that the documentation of diagnostic procedures, including biopsy, was obtained through an examination of medical records. Some diagnostic visits or some biopsies performed during diagnostic visits may have been overlooked. However, quality control procedures ensured that the rate of missing information was low. In addition, by design PLCO only tracked diagnostic procedures that occurred in the year following a positive screen or that led to a cancer diagnosis. Thus, (negative) biopsy occurring 15 months after a baseline positive screen with no or a negative year 1 screen would not be captured. Sensitivity

analyses demonstrated that the effect of these missing intervals on estimated biopsy rates was likely to be low. Another limitation in terms of generalizability is that these men and their physicians were aware that they were participating in a clinical trial, so that their behavior in terms of diagnostic followup and biopsy may have differed from that of men undergoing screening in general practice.

CONCLUSIONS

This study provides data on biopsy rates following a positive PSA or DRE screen in a large, geographically and institutionally diverse sample of American men. Biopsy is more likely following a high screening PSA (greater than 7 ng/ml) that is reproducible and following a positive diagnostic DRE. Whether these biopsy rates represent a medically acceptable level of intervention or they are too low and potentially miss too many cancers cannot be answered at the current time since the overall effect of PSA (and DRE) screening on prostate cancer mortality is unknown. It must await the results of the PLCO trial.

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EDITORIAL COMMENTS

I guess that I am naïve but I was surprised when I read how low the followup testing and biopsy rates were in the PLCO trial after a positive screening PSA or DRE. These authors found that only a little more than half of the men underwent prostate biopsy within 3 years of an abnormal screening PSA of greater than 4.0 ng/ml. Furthermore, of men with abnormal DRE at baseline but normal PSA only about a quarter underwent prostate biopsy by 3 years. Considering that these men were enrolled in a clinical trial and were likely more attuned to health matters, it is surprising that the biopsy outcome is so low. Even in men with high baseline PSA greater than 10 ng/ml figure 1 shows that only about 75% underwent biopsy by year 3.

Population screening for prostate cancer remains controversial in many respects, including efficacy, methodology and costs. This article provides the first broad data on followup of an abnormal screening test that will be useful for cost calculations and other health utilization modeling. While the applicability of the followup testing rates reported compared to those in nonstudy populations is questionable, the overall value of the PLCO trial will be great and I am eagerly awaiting the initial efficacy reports in the next years.

Judd W. Moul
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The authors report early results of the PLCO screening trial in 2,717 men as they relate to prostate biopsies in men with PSA greater than 4 ng/ml. This is an important trial that will produce useful information for years to come. Men with PSA 7 to 10 ng/ml at baseline had much higher biopsy rates than men with PSA 4 to 7 ng/ml, probably because PSA less than 7 ng/ml are more likely to represent benign prostatic hyperplasia. We all look forward to further results from this unique trial.

Thomas A. Stamey
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Will the mortality from prostate cancer be reduced in young men who undergo routine screening, prompt biopsies if an abnormality is identified, and effective therapy if prostate cancer is diagnosed? This is the important question that the $100 million(s) PLCO study was expected to answer. For the reasons outlined below, I am doubtful that it will provide meaningful results.

For many years, I have been concerned about the design of this study. The screening interval of 5 years always seemed to me to be too short. Because death from prostate cancer is the end point, long-term followup will be necessary and I have always questioned why men 70 to 74 years old were included in the study. We now know that death from prostate cancer often occurs after 15 years and it is unlikely that many of these patients will survive long enough to be informative.[1] Finally, and most importantly, because there is no requirement that screened men undergo effective therapy if cancer is found, how can one expect that this study will have a meaningful effect on cancer mortality.[2] Recall, in the studies of breast cancer screening, all women underwent mastectomies.

This article now raises another major question, that is compliance in the screened population. Following a positive screening study, only 19% to 22% of men with a positive DRE and 34% to 41% of men with a PSA of greater than 4.0 ng/ml underwent a prostatic biopsy within 1 year. By 3 years, the comparable numbers were 27% to 28% and 50% to 64%. The authors attempt to justify these low response rates by comparing them to the results from a Prostate Cancer Awareness Week Study (reference 4 in the article). It seems odd to me that the performance of a $100 million National Institutes of Health sponsored grant would be compared to the results from a grass roots organization. Instead, if one looks at the results of the European Randomized Screening for Prostate Cancer Trial (ERSPC), in which screening was done in 7 countries, 84% of the patients underwent a biopsy.[2] It would be more informative if the compliance in the prostate screening arm of the PLCO study were compared to the screened patients in the other 3 arms of the study, ie lung, colon, and ovary. What percent of the patients with positive screening results in these arms of the study were biopsied?

The authors do not explain why the compliance rate was so low. Again, it most likely relates to the design of the study, which in the authors' own words states that "diagnostic followup occurred beyond the control of PLCO and was conducted at numerous sites across the country as part of a pragmatic study design," which they believed was likely representative of clinical practice. In their original power calculations for the sample size was this low biopsy rate taken into consideration.[3] Assuming that this study will be analyzed as intent to treat, what impact will this have on the power of this study to achieve its primary goal? Returning to my initial comments, from what I can tell this study will not provide meaningful information on the value of screening for a young man who responds promptly to abnormal findings and undergoes effective therapy. At best, it may provide some insight into the value of screening in men who were relatively noncompliant in seeking a biopsy and who may not receive effective therapy. Many of us were anxiously awaiting the outcome of this trial. I am no longer holding my breath. Rather, I believe that

our European counterparts have a better chance of providing meaningful information.

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REPLY BY AUTHORS

The PLCO trial was designed to answer the question of whether annual screening of men 55 to 74 years old during a 6-year period, given the prevailing practices of diagnostic followup and treatment in the community, can reduce prostate cancer mortality. Such a pragmatic study design was necessary because study investigators in North America work within a medical system of physician/patient autonomy for decisions, particularly those regarding the choice of diagnostic followup procedures or therapies. The data and analyses in our report indicate that the medical community at large does not view immediate biopsy as the standard of care for all men with positive prostate screens. The pattern of biopsy use we describe clearly shows that physicians are using clinical judgment in determining who should get biopsied. Screening PSA and repeat PSA level, screening and repeat DRE outcome, family history, prior biopsy and other factors related to the perceived likelihood of a biopsy being positive all have a role in biopsy recommendations. In addition, the cost and discomfort of the biopsy and the potential benefits and harm of diagnosing prostate cancer early are also likely to be influencing the physician and patient in deciding whether to proceed with biopsy.

The fact that the general medical community does not view immediate biopsy as a mandatory response to a suspicious screening test should not be surprising. The American urological community as a whole has not uniformly agreed upon a PSA cut point that warrants biopsy. One need only consider the panoply of age and race adjusted PSA reference ranges, the previous studies that have reported little pathological differences among prostate cancers discovered among men with PSA values ranging up to 10 and recent studies that have shown that a considerable proportion of men with low PSA levels have prostate cancer.

Although the European Randomized Study of Screening for Prostate Cancer has higher overall biopsy rates, the screening frequency is lower than that of PLCO (once every 4 years for some European centers). One could argue that this reduced frequency of screening in ERSPC lowers the possible mortality benefit of screening but it also lowers the cost and burden of screening. Careful analysis of the final results from PLCO and ERSPC will likely be informative in determining the relative benefits and costs of prostate cancer screening in various contexts.

Some have claimed that the recent decrease in prostate cancer mortality rates in the United States is due to screening. If this is the case, then presumably the same pattern of diagnostic followup and biopsy as described would be responsible for such a decrease. The power of the PLCO trial to find a significant prostate cancer mortality benefit of screening, if one exists, depends on several factors in the screened and control arms, including the frequency of screening and the rates of biopsy following a positive screen. There is currently no indication, based on the observed prostate cancer diagnosis rates in each study arm, that the power of the PLCO trial with respect to prostate cancer has been unduly compromised due to the pattern of biopsy in men in the screened arm that we describe.